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(54) Complexes of Crown Ethers and Sulfonamides

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SPECIFICATION

1. Title of the Invention

Complexes of Crown Ethers and Sulfonamides

2. Claims

(1) Complexes of 18-crown-6 and sulfonamides.

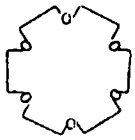
(2) Complexes as described in Claim (1) in which the sulfonamide is sulfamonomethoxine or sulfamethoxazole.

3. Detailed Description of the Invention

Crown ethers, and 18-crown-6 in particular have a large cyclic structure and have the property of forming stable complexes with various types of metal salts and ammonium salts as guest molecules. it is knows that crown ethers form complexes with some organic compounds. In this case, the organic compounds are limited exclusively to aliphatic amines and hydrochlorides thereof [Journal of American Chemical Society, **89**, 7017 (1967)].

The inventors conducted research on complexes of organic medicinal drug products and crown ethers and perfected this invention by discovering that a series of sulfonamides forms stable complexes with 18-crown-6.

Specifically, the present invention relates to complexes of 18-crown-6 and sulfonamides. Here, 18-crown-6 signifies a,1,4,7,10,13,16-hexaoxacyclooctadecane, which is indicated by the following formula.



Further, the sulfonamides are p-aminobenzenesulfonic acid amides or a series of their derivatives, and, in the present invention, include, for example, the following compounds, which are useful as medicinal drugs: Sulfamethoxine, sulfamonomethoxine, sulfadimethoxine, sulfamethoxazole, sulfamethizole, sulfamine, acetosulfamine, sulfaguanidine, sulfathiazole, sulfadiazine, sulfamerazine, sulfamethazine, sulfaisomidine, sulfaisoxazole, sulfamethoxypyridazine, sulfaphenazole.

The following tables show comparisons of changes over time in plasma concentrations of sulfamonomethoxine when a complex of the present invention (sulfamonomethxine/18-crown-6 complex) and when sulfamonomethoxine hydrate were administered orally to Beagle dogs (see the test method described subsequently).

Table I. Changes Over Time in Plasma Concentrations of Unchanged Sulfamonomethoxine

Test material	Changes over time in plasma concentrations (μg/ml)						
	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	24 hr
Sulfamonomethoxine /18-crown-6 complex	26.0 ±7.6	31.8 ±7.3	33.9 ±5.6	39.6 ±5.5	45.1 ±9.8	46.8 ±13	27.9 ±9.2
Sulfamonomethoxine hydrate	0.153 ±0.12	18.8 ±7.1	31.9 ±10	33.6 ±10	35.2 ±12	34.5 ±10	20.3 ±6.6

Table II. Changes Over Time in Plasma Concentrations of Total Sulfamonomethoxine

Test material	Changes over time in plasma concentrations (μg/ml)						
	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	24 hr
Sulfamonomethoxine/18-crown-6 complex	28.0 ±7.5	33.7 ±7.1	37.6 ±5.7	40.6 ±4.2	44.9 ±9.7	49.4 ±13	29.5 ±9.2
Sulfamonomethoxine hydrate	0.540 ±0.36	19.3 ±7.0	33.9 ±10	34.3 ±10	35.0 ±9.9	35.6 ±10	20.9 ±6.8

The physical stability of the complex is also good. The stability of complexes of the present invention in benzene and chloroform obtained in the working examples to be described subsequently or by methods based on them are shown in the following table.

Table III

Sulfonamide	Stability constant (M^{-1})	
	In benzene	In chloroform
Sulfamethoxine	34.30	20.52
Sulfamonomethoxine	165.97	14.11
Sulfamethoxazole	-	10.00
Sulfaphenazole	41.95	6.68
Sulfamethoxypyridazine	29.71	10.60
Sulfadimethoxine	50.38	10.52
Sulfamethizole	-	11.21
Sulfaisoxazole	80.37	13.35
Sulfaisomidine	-	5.44
Sulfamerazine	-	22.38
Sulfathiazole	-	21.08
Sulfanilamide	-	48.54

The complexes of the present invention are stable not only in benzene and chloroform as described above but also in other inorganic solvents such as, for example, carbon tetrachloride and cyclohexane, and, as required, can be isolated from these solvents as solids.

Complexes of the present invention that have been isolated as solids can be administered in unaltered form or can be prepared as suitable solid preparations or semi-solid preparations. Tablets, powders and capsule preparations are suitable as solid preparations. Preparation of these solid preparations can be performed as necessary by standard methods in which lubricants, excipients, binders and disintegrating agents such as magnesium stearate, talc, silicon oxide, starch, lactose, calcium hydrogenphosphate, crystalline cellulose, gum arabic, methyl cellulose, polyvinyl pyrrolidone, gelatin, and carboxymethyl cellulose calcium. Preparation of semi-solid preparations, as necessary, can be performed by standard methods by adding cellulose derivatives such as, for example, Metrose SM (brand name), carboxymethyl cellulose sodium, for example, Celogen F-SB (brand name), hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, and polyvinyl alcohol; oils and fats such as peanut butter oil, coconut oil, Olive oil, soybean oil, rapeseed oil, cottonseed oil, sesame oil, corn oil, rice-bran oil, camellia oil, cacao oil, lard, wool fat and beef tallow, substances obtained by modifying them by hydrogenation, acetylation and cleavage extraction, and aqueous or oleaginous preparations of esters of fatty aids of 6 to 30 carbon atoms and alcohols of 2 to 8 carbons atoms, for example isopropyl myristate (for example, IPM®(EX) manufactured by Nikko Chemicals).

By means of this invention, complexes of various types of sulfonamides and 18-crown-6 can be manufactured as follows.

They can be manufactured by stirring equimolar or excess quantities of 18-crown-6 relative to the sulfonamide in a nonpolar solvent and at room temperatures or lower. The nonpolar solvents that can be used include, for example, benzene, chloroform, carbon tetrachloride and cyclohexane. In executing this method, the sulfonamide is dissolved in the nonpolar solvent, after which 18-crown-6 is added and the mixture is stirred or both the sulfonamide and the 18-crown-6 are stirred in the nonpolar solvent.

The quantity of 18-crown-6 used relative to the sulfonamide is usually an equimolar quantity or a suitable amount greater than that. When 18-crown-6 is used in an excess quantity, for example, more than 20 times the number of moles, a decrease in yield is brought about and complexes of high purity can be obtained.

In order to gather the complex that is produced, the solid substance that is precipitated may be filled, suitably washed and desiccated.

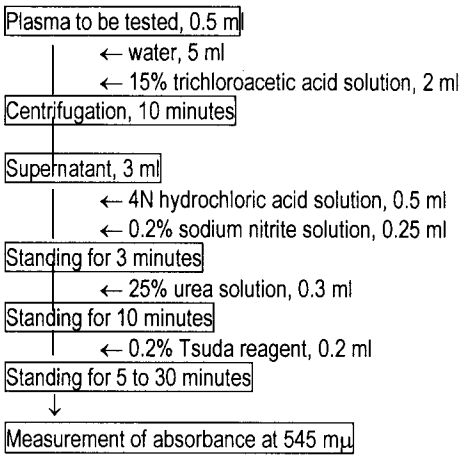
Test Method

Six beagle dogs (male; body weights, approximately, 10 Kg) were divided at random in two groups and administration experiments were performed by cross-over tests. Sulfamonomexine/18-crown-6 complex or sulfamonomethoxine hydrate were administered to 3 animals in each group, and, after 1 week, the test materials were switched and the same test was performed. The test materials, which were powders, were packaged using two wafers and were administered orally. The doses of the test materials were 319.3 mg of sulfamonomethoxine hydrate and 499.2 mg of complex. The beagle dogs were fasted for 24 hours before execution and for 12 hours after execution.

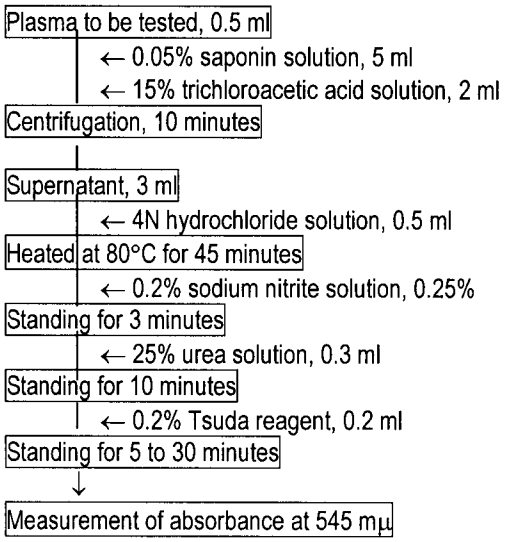
3 ml of blood was collected from the forepaw at 1, 2, 4, 6, 8, 12 and 24 hours after administration. It was centrifuged immediately, the plasma was collected and the blood was frozen and stored at -10°C.

The concentrations of unchanged sulfamonomethoxine and total sulfamonomethoxine in the plasma were measured quantitatively by the modified Bratton-Marshall method. The details of these quantitative determination methods are shown in the figures below.

Quantitative Measurement Method of Unchanged Sulfamonomethoxine in Plasma



Quantitative Measurement Method of Total Sulfamonomethoxine in Plasma



Next, we shall further describe the method of manufacture of the complexes of this invention by presenting working examples.

Working Example 1

Complex of sulfamonomethoxine and 18-crown-6

600 ml of benzene was added to 40 mg of sulfamonomethoxine and 632 mg of 18-crown-6 and the mixture was stirred vigorously for 24 hours at 10°C. The solution was filtered, 888 mg of 18-crown-6 was added to the filtrate and the mixture was shaken for 72 hours at 10°C. The fine crystals that precipitated were washed thoroughly using benzene, after which they were dried under decreased pressure.

Working Example 2

Complex of sulfamonomethoxine and 18-crown-6

100 ml of benzene was added to 4 mg of sulfamonomethoxine and 66 g of 18-crown-6 and the mixture was shaken for 10 days at 10°C. During this period, it was stirred vigorously for approximately 1 hour each day. After 10 days, the complex that was formed was filtered and washed with benzene, after which it was dried under reduced pressure.

Working Example 3

Complex of sulfamethoxazole and 18-crown-6

200 ml of benzene was added to 20 mg of sulfamethoxazole and the mixture was stirred for 24 hours at 10°C. The solution was filtered, 65.27 mg of 1.-8-crown-6 was added to the filtrate and the mixture was shaken for 72 hours at 10°C. The fine crystals that precipitated were filtered and thoroughly washed using benzene, after which they were dried under decreased pressure.

Working Example 4

Complex of sulfamethoxazole and 18-crown-6

100 ml of benzene was added to 5 g of sulfamethoxazole and 6.52 g of 18-crown-6 and the mixture was shaken for 10 days at 10°C. During this period, it was stirred vigorously 1 hour each day. After 10 days, the complex that formed was washed using benzene, after which it was dried under decreased pressure.

Working Example 5

Complex of sulfamethoxypyridazine and 18-crown-6

28.0 mg of sulfamethoxypyridazine and 652.7 mg of 18-crown-6 were used and 28.0 mg of sulfamethoxypyridazine and 105.3 mg of 18-crown-6 were used and were dissolved, respectively, in chloroform and heavy chloroform to make precisely 10 ml.

4. Brief Explanation of the Figures

Figure 1 and Figure 2, respectively, show comparisons of the infrared absorption spectrum of sulfamonomethoxine—18-crown-6 complex (indicated in the figure as (a)) and that of a physical mixture of sulfamonomethoxine and 18-crown-6 (indicated in the figure as (b)), which is a differential scanning thermogram.

Figure 3 through Figure 5, respectively, show the infrared absorption curves of sulfamonomethoxine—18-crown-6 complex (Figure 3), sulfamethoxazole (Figure 4) and –18-crown-6 (Figure 5).

Figure 6 and Figure 7, respectively, show comparisons of the infrared absorption spectrum of sulfamethoxazole—18-crown-6 complex (indicated in the figure as (a)) and that of a physical mixture of sulfamethoxazole and 18-crown-6 (indicated in the figure as (b)), which is a differential scanning thermogram

(temperature elevation rate, 8°/minute and an X-ray diffraction pattern).
[NOTE: The final close parenthesis is missing and is assumed by the translator.]

Figure 8 shows comparisons of partial infrared absorption spectra of complexes of sulfamethoxypyridazine—18-crown-6 (in the figure, (a)-1 indicating a mixture ratio of 0.01 mol : 0.01 mol and (a)-2 indicating a mixture ratio of 0.01 mol : 0.02 mol) in the vicinity of 3400 cm-1 and in the vicinity of 1100 cm-1, with that sulfamethoxypyridazine alone (in the figure, indicated by (c))and that of 18-crown-6 alone (in the figure indicated by (b)).

Figure 9 through Figure 12 show the nuclear magnetic resonance spectra of two types of sulfamethoxypyridazine—18-crown-6 complexes (two types of compounding ratios of sulfamethoxpyridazine and 18-crown-6 of 0.01 mol to 0.04 mol (Figure 9) and 0.01 mol to 0.02 mol (Figure 10)), of 18-crown-6 alone (Figure 11) and of sulfamethoxypyridazine (Figure 12).

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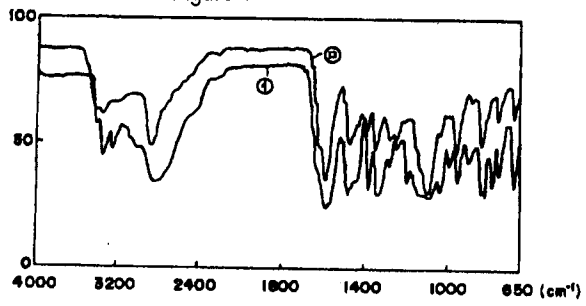
Figure 1



(b)

(a)

Figure 3

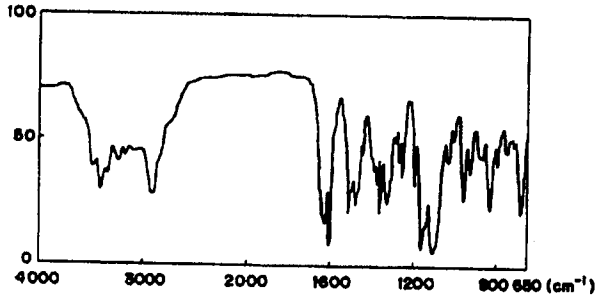
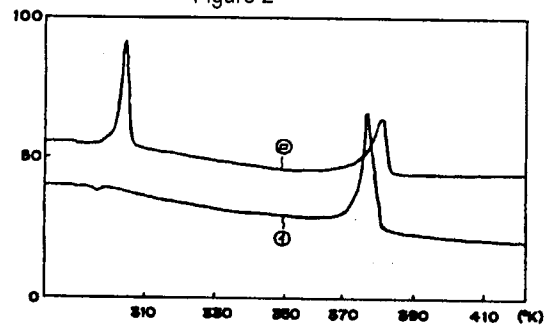


Figure 2



(b)
(a)

Figure 4

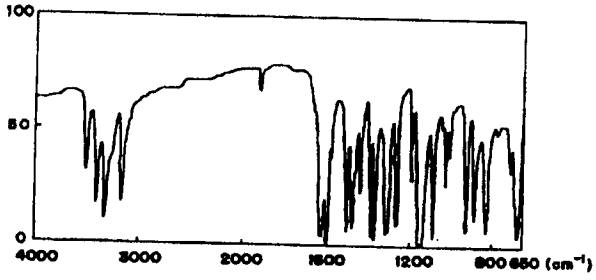


Figure 5

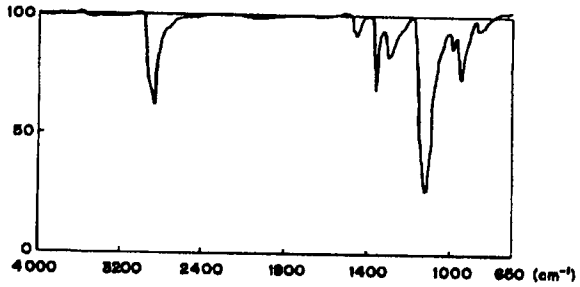
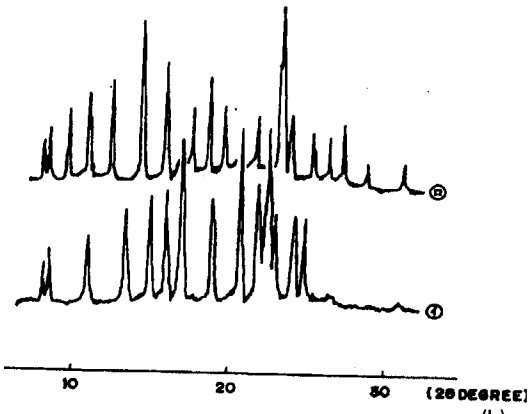
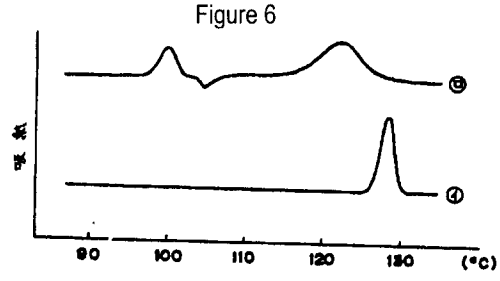


Figure 7



(b)
(a)

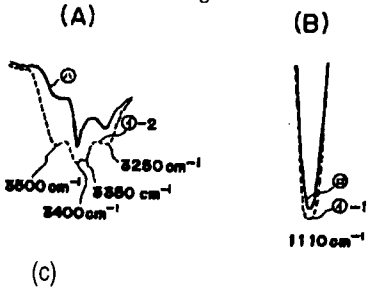
Figure 6



(b)
(a)

(vertical axis) Heat absorption

Figure 8



(c)

(a)-2

(b)

(a)-1

Figure 9

Figure 11

Figure 9

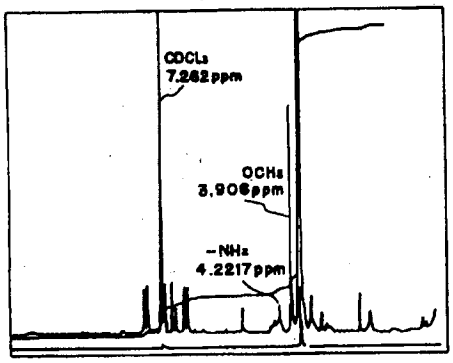


Figure 11

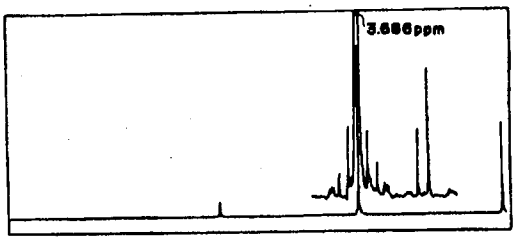


Figure 10

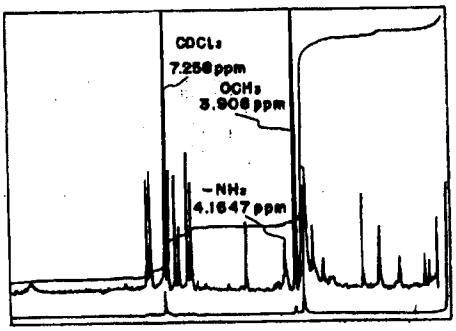
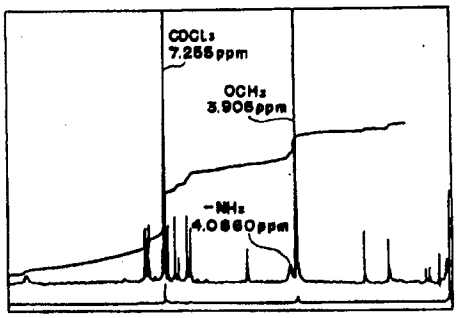


Figure 12



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